Review of Multimodal Therapies for the Treatment of Neuropathic Pain: Clinical Implications

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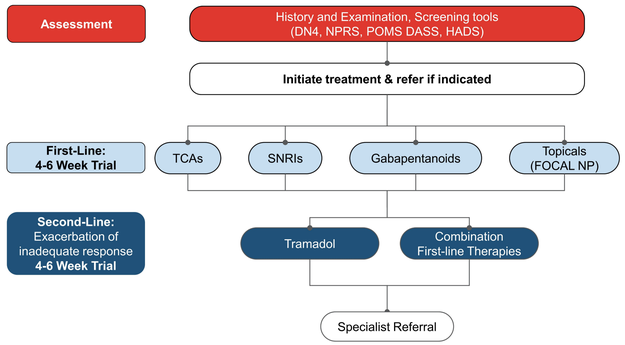
Background

- Neuropathic pain is secondary to many different underlying conditions and has a population prevalence of 7-10%[1]
- With limited choices available, the treatment of neuropathic pain is effective in only 50% of patients,[2] which is due in part to suboptimal efficacy and/or dose-limiting adverse effects (AEs)
- In addition, there has been a decrease in drug effect from recent randomized trials with progressively increasing NNTs[3]
- Combination therapy is thus becoming more common in clinical practice
- Treatment guidelines have recommended combining first-line therapies (Table 1) in patients who do not receive adequate pain relief with single first-line therapies[4] (Figure 1)

Table 1. Summary of Neuropathic Pain Guidelines

	CDC (Centers of Disease Control) 2016[5]	Comprehensive Algorithm on Management of Neuropathic Pain 2019[6]	EFNS (European Federation of Neurological Societies) 2010[7]	NeuPSIG (International Association for the Study of Pain) 2015[8]
Indication	All Neuropathic Pain	All Neuropathic Pain	PHN	All Neuropathic Pain
First Line	Gabapentin Pregabalin TCA's SNRI's **Topical Lidocaine** Topical capsaicin	Gabapentin Pregabalin TCA's SNRI's **Topical Lidocaine** Topical capsaicin	Gabapentin Pregabalin TCA's **Lidocaine plasters**	Gabapentin Gabapentin ER Pregabalin Duloxetine Venlafaxine TCA's
Second Line		Combination of 1st Line Agents Tramadol	Strong Opioids Capsaicin	**Lidocaine patch** Capsaicin patch Tramadol

Figure 1. Algorithm for Management of Chronic Neuropathic Pain of PHN[4]



- Combination therapy can be beneficial when medications are chosen based on differing mechanisms of action, which can often lead to additive or synergistic therapeutic benefits at lower doses and lower toxicity[9]
- Systemic drugs used in the treatment of neuropathic pain have significant CNS-related side effects, while topical agents have primarily local dermal side effects (Table 2)
- Topical agents can be combined with systemic drugs to achieve an additive effect without systemic drug interaction or additional side effects[10]

Table 2. Side Effects Associated with First-Line Therapies for Neuropathic Pain

Medication class	Major/Common side effects	Precautions
TCAs	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol
Gabapentin	Sedation, dizziness, peripheral edema	Renal insufficiency
Pregabalin	Sedation, dizziness, peripheral edema	Renal insufficiency
Topical lidocaine patch	Local erythema, rash	None
Opioids	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	Hx of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant SSRI/SSNRI/TCA use

Objective

- Summarize the safety and efficacy data from 3 gabapentinoid combinations — gabapentinoid + opioid; gabapentinoid + antidepressants; and gabapentinoid + topical lidocaine — and evaluate the benefit-risk from each combination

Methods

- Using a recently published systematic review,[11] we identified combination studies of neuropathic pain. In addition, we reviewed publications of gabapentinoid + topical lidocaine[9,12]

Results

Gabapentinoid + Opioid: 931 participants

- Combination therapy was superior to monotherapy in 4 studies; there was no difference between treatments in 2 studies (Table 3)
- Significant AEs (dizziness, somnolence, constipation, and dry mouth) were noted, as were higher rates of dropouts related to AEs compared to monotherapy in some studies

Table 3. Summary of Gabapentinoid + Opioid Combination Studies

Study	Design	Indication	N	Treatment	Analgesic Efficacy	Safety
Baron 2015	Randomized, controlled, multicenter trial	Low back pain (neuropathic)	313	1. Tapentadol PR + pregabalin 2. Tapentadol PR	No difference	TEAEs: Dizziness and somnolence higher in combination arm (43/159, 27%) than tapentadol arm (26/154, 17%)
Dou 2017	Randomized, controlled, single center, cross-over trial	Neuropathic cancer pain	40	1. Morphine + pregabalin 2. Morphine	Minimal effective dose of morphine significantly lower in combination with pregabalin vs. monotherapy	Combination treatment (pregabalin + morphine) associated with higher frequency of dry mouth and somnolence compared with placebo.
Caraceni 2004	Randomized, controlled, multicenter trial	Neuropathic cancer pain	121	1. Gabapentin + opioid 2. Opioid	Average pain score significantly reduced in combination arm vs. monotherapy	Dropouts due to AEs: 6/80 in combination group vs 3/41 in monotherapy group
Gilron 2005	Randomized, controlled, single center, cross-over trial	DPN, PHN	57	1. Gabapentin + Morphine 2. Gabapentin 3. Morphine 4. Placebo	Mean daily pain score significantly lower in combination group vs monotherapy groups	Combination groups had higher rates of constipation and dry mouth compared with monotherapy groups
Hanna 2008	Randomized, controlled, multicenter trial	DPN	338	1. Gabapentin + Oxycodone 2. Gabapentin	Pain scores significantly reduced in combination group vs. monotherapy	Combination group had higher rates of constipation, nausea, vomiting, dizziness, fatigue and somnolence. Combination group had higher rate of drop outs due to AEs (27/169) vs. monotherapy (9/169)
Zin 2010	Randomized, controlled, single center	DPN, PHN	62	1. Pregabalin + Oxycodone 2. Pregabalin	No difference	Drop outs because of AEs: 4/29 in combination group

Gabapentinoid + Antidepressant: 472 participants

- Combination therapy was superior to monotherapy in 2 studies; ; there was no difference between treatments in 1 study (Table 4)
- Dropouts due to AEs were higher and dry mouth was more frequent with combinations in 1 study; in another, the treatments were comparable

Table 4. Summary of Gabapentinoid + Antidepressant Studies

Study	Design	Indication	N	Treatment	Analgesic Efficacy	Safety
Holbech 2015	Randomized, controlled, multicenter, crossover trial	Polyneuropathy	73	1. Pregabalin +imipramine 2. Imipramine 3. Pregabalin 4. Placebo	Combination arm had lower pain score than monotherapy arms	Dropouts due to AEs higher on combination arm (7/73) vs imipramine (3/73), pregabalin (2/73), or placebo (1/73). Frequent AEs include: tiredness, dizziness and dry mouth
Tesfaye 2013	Randomized, controlled, multicenter trial	DPN	343	1. Pregabalin + duloxetine 2. Duloxetine 3. Pregabalin	No difference	No statistically significant differences between treatment groups for TEAE.
Gilron 2009	Randomized, controlled, single-center trial	PHN, DPN	56	1. Gabapentin + nortriptyline 2. Nortriptyline 3. Gabapentin	Mean daily pain intensity was significantly lower during combination treatment vs either monotherapy	At maximum tolerated dose, dry mouth was significantly more frequent with nortriptyline or combination than gabapentin

Gabapentinoid + Lidocaine Patch: 205 participants

- Combination therapy was effective at reducing pain from baseline in 2 open-label studies (Table 5)
- The incidence of AEs was low, and events were typically mild to moderate

Table 5. Summary of Gabapentinoid + Lidocaine Patch Studies

Study	Design	Indication	N	Treatment	Analgesic Efficacy	Safety
Rehm 2010	Randomized, open-label, multicenter, non-inferiority study	PHN	98	1. Pregabalin + Lidocaine patch 2. Pregabalin	49% reduction in pain intensity with combination treatment (vs. monotherapy baseline)	Drug-related AEs occurred in 5.9% of patients with combination treatment (PL), most of them related to pregabalin
White 2003	Open label, non-randomized, multicenter trial	PHN, DPN, LBP	107	1. Gabapentin + Lidocaine patch	BPI scores for worst, least, average, pain right now, and pain relief scores significantly lower compared with baseline	The most frequently reported treatment-related AEs were somnolence (1.9%), paresthesia (1.9%), and dermatitis (1.9%). All treatment-related AEs were mild to moderate.

Conclusions

- **Combinations of systemic agents (gabapentinoid + opioid or antidepressant) were associated with significant AEs and dropouts.**
- **Combinations of a systemic and topical agents (gabapentinoid + topical lidocaine) can improve efficacy with minimal additional AEs.**
- **Topical agents with minimal systemic AEs — such as lidocaine patch, which has shown benefits in many neuropathic pain conditions — can improve the likelihood of achieving meaningful pain relief when used as adjuvant therapy**

Disclosures: SN is a paid consultant of Scilex Holding Company, manufacturer of lidocaine topical system 1.8%; EKC and DL are employees of Scilex Holding Company, manufacturer of lidocaine topical system 1.8%.

References: 1. *Neurology*. 2007;70:1630-1635; 2. *J Clin Med*. 2021;10:3533; 3. *Pain*. 2018;159:2339-2346; 4. *Pain Med*. 2019;20(suppl 1):S2-S12; 5. https://www.cdc.gov/opioids/providers/prescribing/clinical-tools.html; 6. *Pain Medicine*. 2019:S2-S12; 7. *European J Neurol*. 2010:17:1113-1123; 8. *Lancet Neurol*. 2015:14(2):162-173; 9. *Pain Med*. 2003;4(4):321-330; 10. *Curr Med Res Opin*. 2010:26(7):1607-1619; 11. *Pain*. 2022;00:1-22; 12. *Curr Med Res Opin*. 2010;26(7):1607-1619.